GUIDANCE[1]

CEFACLOR CAPSULES AND SUSPENSIONS

IN VIVO BIOEQUIVALENCE

AND *IN VITRO* DISSOLUTION TESTING

I. INTRODUCTION

A. Clinical Usage/Pharmacology

Cefaclor is a cephalosporin antibiotic which inhibits bacterial cell-wall synthesis in a manner similar to that of penicillin (1). Cefaclor is used in the treatment of otitis media caused by susceptible *Streptococcus pneumoniae*, *Haemophilus influenzae* (including ampicillin-resistant strains), group A β-hemolytic streptococci or staphylococci; lower respiratory tract infections (including pneumonia) caused by susceptible *S. pneumoniae*, *H. influenzae*, or group A β-hemolytic streptococci; upper respiratory tract infections (including pharyngitis and tonsillitis) caused by susceptible group A β-hemolytic streptococci; urinary tract infections (including pyelonephritis and cystitis) caused by susceptible *Escherichia coli*, *Proteus mirabilis*, klebsiella, or staphylococci; or skin and skin structure infections

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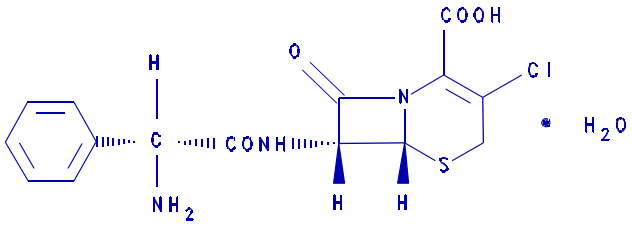
[1] This statement, prepared by the Division of Bioequivalence in the Office of Generic Drugs, is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research, Food and Drug Administration, to the views expressed. For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (Phone: 301-295-8290; Fax: 301-295-8183).

caused by susceptible *Staphylococcus aureus* or group A β-hemolytic streptococci (1,2).

Currently, cefaclor is marketed by Eli Lilly under the name Ceclor ®, 250 mg and 500 mg capsules, and as a powder for reconstitution as suspension for oral administration, 125 mg/5 mL, 187 mg/5 mL, 250 mg/5 mL and 375 mg/5 mL. The usual adult dosage is 250 mg every 8 hours. For more severe infections (such as pneumonia), doses may be doubled.

B. Chemistry

Cefaclor is a semisynthetic cephalosporin antibiotic and has the following chemical structure:



Cefaclor

The drug occurs as a crystalline powder and is sparingly soluble in water. Cefaclor is most stable in the acid pH range at a temperature of 4 °C. Cefaclor capsules should be stored in tight containers at a temperature less than 40 °C, preferably between 15 and 30°C.

C. Pharmacokinetics

Cefaclor is well absorbed after oral administration to fasting subjects. Total absorption is similar regardless whether the drug is given with or without food. When it is taken with food, the peak concentration achieved is 50% to 75% of that observed in fasting subjects and generally appears about 1 hour later.

Following administration of 250 mg, 500 mg, and 1 g doses in fasting subjects, average peak serum levels of approximately 7, 13, and 23 µg/mL, respectively, were obtained within 30 to 60 minutes. Approximately 60% to 85% of the drug is excreted unchanged in urine within 8

hours, the major portion being excreted within the first 2 hours. The serum elimination half-life in subjects with normal renal function is 0.6 to 0.9 hour. In patients with severely reduced renal function, the plasma elimination half-life of the drug is 2.3 to 2.8 hours. Hemodialysis shortens the half-life by 25% to 30% (3).

II. *IN VIVO* BIOEQUIVALENCE STUDIES[2]

A. Product Information

1. FDA Designated Reference Product: i) Ceclor [R] 500 mg capsule, ii) 375 mg/5 mL for suspension, manufactured by Eli Lilly.

2. Batch size: The test batch or lot must be manufactured under production conditions and must be of a size at least 10% that of the largest lot planned for full production or a minimum of 100,000 capsules, whichever is larger .

3. Potency: The assayed potency of the reference product should not differ from that of the test product by more than 5%.

B. Types of Studies Required

1. A single-dose, randomized, two-period, two-treatment, two-sequence crossover study under fasting condition comparing equal (1x500 mg) for capsule and 375 mg/5 mL for suspension of the test and reference products.

2. A single-dose, randomized, three-treatment, three-period, six-sequence, crossover, limited food effects study comparing equal doses of the test and reference products when administered immediately following a standard breakfast.

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[2] The sponsoring firm is advised that an Investigational New Drug Application (IND) filing may be required if dosing levels exceed those recommended in the official labeling. Please refer to 21 CFR 312.2, 320.31(b)(1) and also Office of Generic Drugs Policy and Procedure Guide #36-92, Submission of an "Investigational New Drug Application" to the Office of Generic Drugs, issued October 13, 1992.

C. Recommended Protocol for Conducting a Single Dose Bioequivalence Study Under Fasting Condition

Objective: To compare the rate and extent of absorption of a generic formulation with that of the reference formulation when given as equal labeled doses.

Design: The study design is a single dose two-treatment, two-period, two-sequence crossover with a one week washout period between Phase I and Phase II dosing. Equal number of subjects should be randomly assigned to the two possible dosing sequences. Before initiation of the study, the proposed protocol should be approved by an institutional review board.

Facilities: The clinical and analytical laboratories used for the study should be identified along with the names and titles and curriculum vitae of the medical and scientific/ analytical directors.

Selection of Subjects: The sponsor should enroll a number of subjects sufficient to ensure adequate statistical results. It is recommended that a minimum of 24 subjects be used in this study. Subjects should be healthy male volunteers 18-50 years and within 10% of ideal body weight for height and body build (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Subjects should be selected on the basis of acceptable medical history, physical examination, and clinical laboratory test results. Subjects with any current or past medical condition which might significantly affect their pharmacokinetic or pharmacodynamic response to the administered drug should be excluded from the study. Written, informed consent must be obtained from all study participants before they are accepted into the study.

Procedures: Following an overnight fast of at least 10 hours, subjects should be administered a single dose of the test or reference product with 240 mL of water.

Restrictions: Study volunteers should be subject to the following restrictions:

a. Water may be allowed except for one hour before and after drug administration when no liquid

should be permitted other than that needed for drug dosing.

b. Subjects should fast for at least four hours after administration of the test or reference treatment. All meals should be standardized during the study.

c. No alcohol or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

d. Subjects should take no RX or OTC medications beginning two weeks before drug administration until after the study is completed.

Blood Sampling: Venous blood samples should be collected pre-dose (0 hours) and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 3, 4, 5, 6, and 8 hours post-dose. Due to the chemical instability of cefaclor, the blood samples should be analyzed as soon as they are drawn or plasma samples should be promptly frozen at -70 °C until analysis. Following a one week washout period, subjects should begin Study Phase Two. For each subject, the sponsor should state the time elapsed between sample collection and sample assay. An explanation should be given for any missing samples.

Subject Monitoring: **Blood pressure and pulse rate should be monitored during the blood sampling periods. Any subject with a heart rate greater than 120 bpm should have an electrocardiogram performed and have his pulse monitored hourly. Subjects should report any unusual symptoms observed during the study.**

Analytical Methods: For the measurement of cefaclor in plasm**a samples, a microbiological assay, HPLC method or other suitable method should be selected (4). The method used** should be described in detail and references, if any, should be cited. The method should include detailed calculation procedures for the assay results. In general, the sponsor should select a method fully validated with respect to adequate sensitivity, specificity, linearity, recovery, and accuracy, and precision (both within and between days). Stability of the analyte in plasma samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. It

should be noted that cefaclor is most stable in the acid pH range at a temperature of 4 °C. For analytical work cefaclor stock solutions should be prepared fresh daily in pH 4.5 buffer (5).

Chromatograms of the analysis of the unknown samples, including all associated standard curve and quality control chromatograms, should be submitted for one-fifth of the subjects, chosen at random. The sponsor should justify the rejection of any analytical data and provide a rationale for selection of the reported values.

Statistical Analysis of Pharmacokinetic Data (Blood Plasma/Serum): See Division of Bioequivalence Guidance, "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design."

Clinical Report and Adverse Reactions: Medical histories, physical examination reports and all incidents of possible adverse reactions to the study formulations for subjects in the study should be reported.

D. Limited Food Effects Study

The limited food effects study should be performed in the same manner as the single-dose study under fasting condition, with the following exceptions:

Procedures: Equal numbers of subjects should be assigned to each of the six dosing sequences possible in a three-treatment, three-period study design (total 18 subjects). Each subject will receive the following treatments:

Treatment 1: Generic Product, 1x500 mg Cefaclor capsule or 375 mg/5 mL suspension administered after standard breakfast [3]

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[3] Each subject should consume a standardized, high fat content meal consisting of:

One buttered English muffin
One fried egg
One slice of American cheese
One slice of Canadian bacon
One serving of hash brown potatoes

Treatment 2: Reference Product, 1x500 mg Ceclor® capsule or 375 mg/5 mL suspension (Eli Lilly) administered after standard breakfast

Treatment 3: Generic Product, 1x500 mg Cefaclor capsule or 375 mg/5 mL suspension dosed fasted

Following a ten hour fast, the subjects receiving the fed treatments should be served a standard breakfast. The subjects should have thirty minutes to finish the entire breakfast, then be immediately dosed with Treatment 1 or 2, above, taken with 240 ml of water. Subjects receiving the treatment under fasting condition
should be dosed with Treatment 3, taken with 240 ml of water only. The same lots of the test and reference products should be used as in the fasted study, above. No food should be allowed for at least 4 hours post-dose with water allowed after the first hour. Subjects should be served scheduled standardized meals throughout the study.

Statistical Analysis: In general, a comparable food effect will be assumed provided the AUC_{0-T}, $AUC_{0-\infty}$, and C_{max} mean values for the test product differ no more than 20% from the respective mean values obtained for the reference product in this study.

Retention of samples: The laboratory conducting the bioequivalence testing should retain an appropriately identified reserve sample of the test product and reference standard used to perform an in vivo bioequivalence study for approval of the application. Each reserve sample should consists of at least 200 dosage units. For more information on retention of bioequivalence samples please refer to CFR 21,320.32.

III. *IN VITRO* TESTING REQUIREMENTS

A. Dissolution Testing

Conduct dissolution testing on 12 dosage units of the test product versus 12 units of the reference product.

Eight fluid oz. (240 mL) of whole milk
Six fluid oz. (180 mL) of orange juice

The biostudy lots should be used for those product strengths tested *in vivo*. Their is currently no official USP dissolution method available for this product. Therefore, the following method is to be used *on an interim basis*, until such time that an official USP method is published:

Apparatus:	USP XXII apparatus 2 (paddle)
RPM:	50
Medium:	deaerated water
Volume:	900 mL
Sampling Times:	10, 20, 30 and 45 minutes
Tolerance (Q):	NLT 80% in 30 minutes
Analytical:	U.V. abs. @ ca. 264 nm, or other validated method

The percent of label claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

B. Content Uniformity Test

Content uniformity testing on the test product lots should be performed as described in USP XXII.

IV. WAIVER REQUIREMENTS

A. Waiver of *in vivo* bioequivalence study requirements for the 250 mg strength of the generic product may be granted per 21 CFR 320.22(d)(2) provided both of the following conditions are met:

1. The 250 mg capsule is formulated proportionally similar in both active and inactive ingredients to the firm's 500 mg capsule which has been demonstrated to be bioequivalent to the reference product *in vivo.*

2. The 250 mg capsule of the generic product meets the dissolution testing requirements.

B. Waiver of *in vivo* bioequivalence study requirements for the powder for reconstitution as suspension for oral administration, 125 mg/5 mL, 187 mg/5 mL, and 250 mg/5

mL strengths of the generic product may be granted per 21 CFR 320.22(d)(2) provided both the following conditions are met:

1. The 125 mg/5 mL, 187 mg/5 mL, and 250 mg/5 mL suspensions are proportionally similar in their active and inactive ingredients to the firm's 375 mg/5 mL suspension.

2. An acceptable *in vivo* bioequivalence study has been conducted for the 375 mg/5 mL suspension.

V. REFERENCES

1. Gilman AG, Goodman LS, Rall TW, Taylor P. Goodman and Gilman's the pharmacological basis of therapeutics. 8th ed. New York: Pergamon Press 1990:1085-92.

2. American hospital formulary service drug information '90. Bethesda, Maryland: American Society of Hospital Pharmacists, 1990:87-9.

3. Physicians' desk reference. 46th ed. Montvale, New Jersey: Medical Economics Company, 1992:1251-2.

4. Nahata MC. Determination of cefaclor by high-performance liquid chromatography. J Chromatogr 1982;228:429-33.

5. Foglesong MA, Lamb JW, Dietz, JV. Stability and blood level determinations of cefaclor, a new oral cephalosporin antibiotic. Antimicrob Agents Chemother 1989;13:49-52.

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